

Collaborative and Partnership Opportunities in the Area of Research and Development for Paediatric Antiretroviral Drugs for Low Income Countries

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Declaration of own work

The author declares that the research presented in this report is his own, that the data used in the analysis was collected by himself, analyzed by himself and that the conclusions drawn and recommendations made are his own. Furthermore, he declares that the participants in the study gave informed consent to participate.

Acknowledgement:

The author would like to acknowledge the contribution of all of the interviewees without whose time and willingness to participate, this study would not have been possible. They are listed in the “method” section of the report. The author would also like to express his appreciation to Dr Shipham for this guidance in putting this research project together.

Executive Summary

This research was motivated by the urgent need for global health institutions like the World Health Organization and UNITAID to adopt an informed, market based approach to engaging with the research and development pipeline for drugs that treat children infected with the HIV virus. As the market size for these products declines over the next decade, the usual incentives for pharmaceutical and biotech companies to invest in the development of new drugs and new formulations of existing drugs is likely to dwindle. Innovated solutions are needed if a business case is to be made that addresses this important public health need.

The objectives of the research include firstly, describing the public health need for research and development into paediatric Antiretroviral drugs; secondly describing the various stakeholders and their interests; and finally exploring and identifying potential collaborative / partnership opportunities that can be employed to address the existing public health need while satisfying the various stakeholder interests at play.

The study methods employed included conducting twelve in-depth interviews with key informants from the public and private sector. All interviews were recorded and transcribed before an iterative content analysis was done to categorize themes and issues raised. The data collected was triangulated with understanding gained from a literature review that considered 29 peer reviewed papers and with data collected from key documents available on the webpages of relevant institutions.

Reflecting on the results of this study, the author argues that there is a pressing public health need for both new paediatric Antiretrovirals and new formulations of existing paediatric Antiretrovirals. The most effective way for this public health need to be addressed, however, is through proactively engaging the market dynamics that drive research and development for these products.

Limited market incentives and prohibitive regulatory constraints represent the major barriers to investment in this area. Partnership opportunities exist however that could make the market for paediatric Antiretrovirals more attractive to industry through risk and cost sharing with the public sector. Success in the area of product development for TB and malaria suggest that these mechanisms are both viable and desirable.

Initiatives whereby the public sector share in the research and development costs (by providing capital) and risks (by providing reward incentives and advanced market commitments) in exchange for price concessions in place of strategic public health importance, could facilitate research and development in the area of paediatric Antiretrovirals.

This report recommends that multilateral donor organizations (like UNITAID) engage directly with the pharmaceutical industry by creating a Health Impact Fund (that rewards industry for changes in health outcomes), Advanced Market Commitments (for products of strategic public health importance) and work with venture capital firms by providing security for money provided to pharmaceutical companies that is invested in research and development for paediatric Antiretrovirals.

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Abbreviations

ABC	Abacavir (an antiretroviral drug)
AMC	Advanced Market Commitments
ARVs	Antiretroviral drugs
AZT	Zidovudine (an antiretroviral drug)
CHAI	Clinton HIV Access Initiative
FDCs	Fixed Dose Combinations
GMP	Good Manufacturing Practice
IAVI	International AIDS Vaccine Initiative
IPR	Intellectual Property Rights
PPP	Public Private Partnership
PDP	Product Development Partnership
MMV	Medicines for Malaria Venture
MPP	Medicines Patent Pool
MTCT	Mother to Child Transmission of HIV
NVP	Nevirapine (an antiretroviral drug)
PE	Private Equity
PMTCT	Prevention of Mother to Child Transmission of HIV
R&D	Research and Development
SVC	Social Venture Capital
TRIPS	Trade Related aspects of Intellectual Property
VC	Venture Capital
WACC	Weighted Average Cost of Capital
WHO	World Health Organization
WTO	World Trade Organization
3TC	Lamivudine (an antiretroviral drug)

Chapter 1 Problem in context / Orientation

1.1 Introduction

Infants who contract HIV during the birth process or breastfeeding are no longer necessarily condemned to die. Medicines in the form of Antiretrovirals (ARVs) that can prolong their lives into adulthood are available. The emergency of resistant strains of HIV and the various constraints that exist when treating a child (the need for liquid formulations for very young children for example) means that ongoing research and development (R&D) of paediatric ARVs is extremely important if the millions of children who are currently HIV positive are to be effectively treated.

Market incentives for the pharmaceutical industry to invest in ongoing R&D in this area are weak and dwindling. This is partly due to the fact that most HIV positive children live in poor countries where large profit margins are not feasible. Added to this, the World Health Organization (WHO) together with UNICEF have committed to “virtual elimination” of Mother to Child Transmission (MTCT) of HIV by the year 2015. While this is a laudable endeavor, it does mean that the market size for paediatric ARVs is set to become significantly small over the next decade, which further erodes the prospect of future returns on investments in R&D in this area.

Given this imperative this research project explores the institutional and economic landscape of R&D into paediatric ARVs with a view to identifying partnership opportunities between pharmaceutical companies and global health institutions like the World Health Organization and UNITAID that address the R&D pipeline for these products.

1.2 Problem in Context / Orientation

An estimated 2.5 million children are living with HIV of which 2.3 million are in sub-Saharan Africa. Approximately 1,000 children are infected with HIV every day, mostly during childbirth and breastfeeding. Of those infected, only about

360,000 are currently being treated - although this number is up from 75,000 in 2005 (WHO, 2011). The World Health Organization has set the goal of virtually eliminating mother to child transmission globally by the year 2015 by providing medicines for HIV positive pregnant women that prevents the transmission of the virus. While the decline in the incidence of new HIV cases in children is laudable, it does have implications for the market incentives that drive R&D in the pharmaceutical industry. As fewer children have HIV, the development of appropriate treatments for those that do could become less and less.

The issue of drug development for people in poor countries is subject to the business reality of the pharmaceutical industry and the incentives that drive its R&D agenda. Between 1975 and 1999, out of 1,393 new drugs developed, only 13 (less than 1%) were designed to treat tropical diseases, which account for more than 90% of the world's disease burden. More emphatically, only 10% of the USD 70 billion spent on health research worldwide each year is for research into health problems that affect 90% of the world population - the 90/10 gap (Hale et al. 2005). These facts highlight the dramatic mismatch between global resource expenditure and public health needs in poor countries.

This problem is compounded by poor market characterization, poor demand forecasting, prohibitive regulatory constraints and intellectual property rights (IPR) issues that make the development of these products unattractive from a commercial point of view. By exploring similar R&D problems for other "neglected tropical diseases" and by understanding the various incentives that drive the respective stakeholders (public and private), potential partnerships and collaborative opportunities may exist that allow for scenarios that are both profitable to pharmaceutical companies and meet important public health needs in this area.

Buse and Harmer (2007) describe Global Health Partnerships as "collaborative relationships among pharmaceutical companies in partnership with UN-based organizations, developing country governments and public and

private foundations to ensure efficient product development, healthcare delivery and technical support for implementation of national disease programmes” (Kent Buse & Harmer 2007)

1.3 Problem review

In order for global health institutions like the WHO to work towards their strategic objective of ensuring access to life saving drugs for children in the world poorest areas, they need to engage the complexity of a disparate set of stakeholders with varying interests and objectives. The complexity of this problem can be thought of as existing within three interrelated domains:

1. understanding the unmet public health need (demand)
2. understanding the various stakeholder interests (supply)
3. identifying opportunities for partnerships and collaborative initiatives that align public health needs (demand) with stakeholder interests (supply).

Figure 1.1. below illustrates these three domains of complexity and represents a framework for unpacking the problem in greater detail.

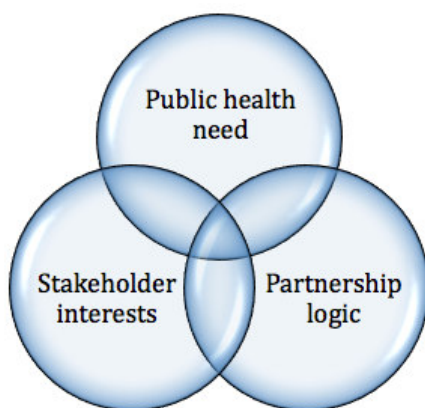


Figure 1.1. Framework for considering R&D of paediatric ARVs

Relevant constructs:

Public health need: a starting point for any initiative aimed at improving the availability of paediatric drugs in poor countries must be to understand the existing ‘unmet’ need globally. The demand for these products should be described in terms of its magnitude at a point in time, but rather in terms of the

needs that will emerge over the coming decade. Due to lack of infrastructure and sophisticated health information systems, demand forecasting for these products is currently extremely weak in poor countries.

Stakeholder interests: pharmaceutical companies, public research organizations, multilateral donor agencies and global health institutes have distinct but not mutually exclusive strategic objectives. While the private sector needs to ensure that it maximizes its shareholder value, public institutions want to ensure access to lifesaving treatment for as many children as possible.

Partnership logic: opportunities for risk and cost sharing in exchange for price and market concessions have been used to promote the development of treatments for neglected diseases in the past. This report will consider such collaborative opportunities in the area of paediatric ARVs.

1.4 Problem statement

Medical interventions in the developing communities are dogged by a number of issues not least of which are basic business realities. One is therefore often faced with business reality vs medical need paradox and it is this paradox that is at the center of this research.

This research explores the institutional and economic landscape of R&D with a view to identifying partnership opportunities between pharmaceutical companies global health institutions like the World Health Organization and UNITAID that address the Research and Development pipeline for paediatric Antiretroviral medications.

The thesis postulated here is:

The current institutional and economic landscape of R&D needs partnership opportunities between pharmaceutical companies and global health institutions like the World Health Organization and UNITAID that address the Research and Development pipeline for paediatric Antiretroviral medications

1.5 Objectives

Objective 1 – public health need

To characterize the market place for paediatric ARVs including what products are needed and why it is that the demand for these products is likely to change over the next decade.

Objective 2 – stakeholder interests

To identify the various stakeholders, both in the global health arena and the private sector and identify their interests and strategic objectives.

Objective 3 – partnership logic

To explore opportunities for collaboration and partnership between the various actors so as to meet both the public health need and the various stakeholder interest identified though [1] and [2] above.

1.6 Importance of the research

Organizations like the World Health Organization and UNITAID that have a public health mandate cannot achieve their goals without working closely with the private sector. By looking at a public health objective (in this case, ensuring access to life saving medicines for children in poor countries) through the lenses of business science research enables all stakeholders to make informed (evidence based) decisions as to how their strategic objectives can be met.

Importantly, this research seeks to describe and understand the R&D landscape, which in turn should provide a platform upon which innovative solutions can be explored. The importance of this research lies in the implications for both children living with HIV and for organizations (public and private) seeking to find 'win-win' collaborative opportunities.

1.7 Assumptions

The conclusions and recommendations of this research makes the assumptions that firstly, the political will exists within large public health institutions like the World Health Organization to engage more proactively with the private sector and secondly that the private sector are willing to explore innovative partnership arrangements that serve a public health agenda. Each of the stakeholders act within a complex landscape of political and economic realities. Broad buy-in from a disparate array of decision makers is necessary if any meaningful collaborative initiatives are to be engaged.

1.8 Delimitations (scope)

This research explores the nature of existing and potential partnerships and collaborative opportunities in the area of paediatric ARVs. It seeks to understand the political and economic landscape within which decisions get made and draws inference as to what additional opportunities might exist that have as yet not been exploited in realm.

1.9 Limitations

This research does not unpack the complexities of internal political and organizational structural issues that contribute towards individual organization decisions making as it pertains to partnership creation. The research method also has limitations that are described in more detail in chapter 4.

1.10 Overview of the report

Chapter 1. Problem in context: This chapter describes the objectives of this research in the context of background and overall context in which the paediatric ARV crisis exists.

Chapter 2. Problem analysis / Theoretical considerations: This chapter makes the link between the research question under consideration and existing business science, in particular market dynamics and stakeholder power.

Chapter 3. Literature review: This chapter identifies the existing body of knowledge that has been published in the areas of the need for paediatric ARVs, stakeholder interests and partnership logic. It represents a platform from which well informed data collection could take place and is in-and-of

itself an important source of information that contributes towards the broader analysis done in this research

Chapter 4. Research design and methods: This chapter outlines the research design and scientific methods applied in such a way as to make the data collection both repeatable and reliable as far as possible.

Chapter 5. Results and discussion: This chapter lays out the results of the data collection and explores the relationship between the data and the research objectives.

Chapter 6. Conclusions and Recommendations: This chapter reflects on the data and considers the potential implications therein. It also makes recommendations.

Chapter 7. Reference

Appendices

1.11 Summary of chapter 1

Chapter 1 has provided a description of the problem that this research seeks to unpack and explore. The need for ongoing R&D in the area of paediatric ARVs is essential if the millions of children with HIV are to be effectively treated. Market incentives for industry to invest in this kind of research is limited and the need for innovative collaborative initiatives between the public and private sector are needed if this agenda is to be pursued.

The objectives of the research include firstly, understanding and describing the public health need for R&D into paediatric ARVs; secondly understanding and describing the various stakeholders and their interests; and finally exploring and indentifying potential collaborative / partnership opportunities that can be employed to address the existing public health need while satisfying the various stakeholder interests at play.

Chapter 1 concludes by highlighting that the importance of this research lies in the potential for win-win opportunities but states the caveat that these opportunities can only be exploited if the willingness to engage them exists within the current political and economic environment.

Chapter 2 Problem analysis / Theoretical considerations

2.1 Introduction

A broad viewpoint of the major issues relevant to this research has been depicted in Chapter 1 above. In order to provide context to the discussion on this subject it is important to consider two important tenants of business theory, i.e. market dynamics and stakeholder power. Chapter 2 will outline two important aspects of business theory that underpin and inform the data collection and analysis.

2.2 Theoretical Consideration 1: Market dynamics

The economist Milton Friedman stated that **“the business of business is business”** (Friedman 1962). Supporting this, Sloan states that **“the strategic aim of a business is to earn a return on capital”** (Sloan et al. 1998). Many have argued that there is a moral and economic imperative for managers to focus on profit maximization (Minford 1998) (Grant 2001) (Porter 2004).

These positions are counterbalanced by Drucker: **“So we should think through what management should be accountable for; and how and through whom its accountability can be discharged. The stockholders interest, both short and long term is one of the areas. But it is only one.”** (Drucker 1988)

Within the current paradigm of capitalism and free markets, the private sector is largely left to follow its own interest with the understanding that good and services are efficiently provided for in the right quantity and at a price that is agreeable to the consumer. Public sector intervention is only called for where market mechanisms fail act in the interest of the public at large. Adam Smith (1776) in “An Inquiry into the Nature and Causes of the Wealth of Nations” describes how the invisible hand of the market leads to an efficient quantity and price equilibrium as a function of supply (the marginal cost of production)

and demand (the marginal benefit of consumption) - see figure 2.1. Below (Smith, 1776)

Understanding the theoretic considerations that lead to this equilibrium is useful in the context of addressing market failure. Various parameters relevant to this research problem will be unraveled here.

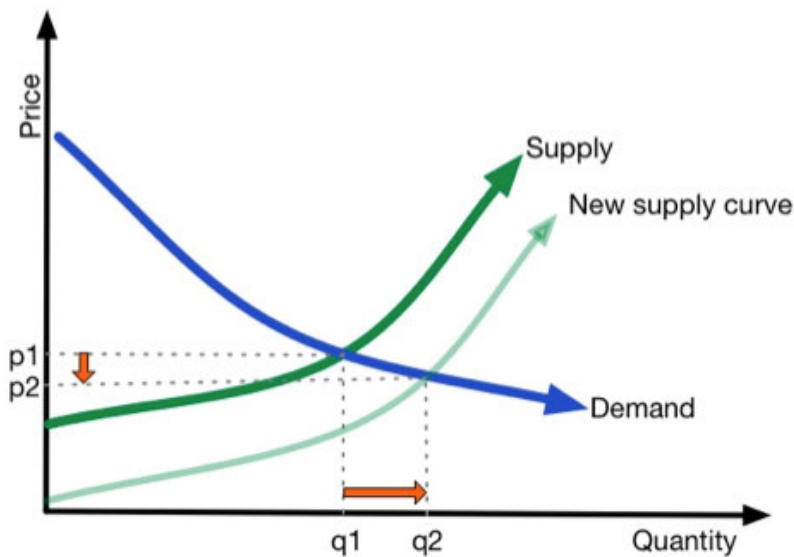


Figure 2.1. Market dynamics – a normative model

While a detailed discussion on the market dynamics for drugs in low income countries is beyond the scope of this report, in order to provide context for the particular area of interest to this study, it is worth considering briefly how it is that this normative model applies in this area. Figures 2.2, 2.3 and 2.4. below show how a normative demand curve for drugs in developing countries is relatively 'L' shaped and that with the intervention of multilateral donor agencies like UNITAID who provide finance for drugs with a view to making them more accessible, the demand curve is stretched out and becomes more linear.

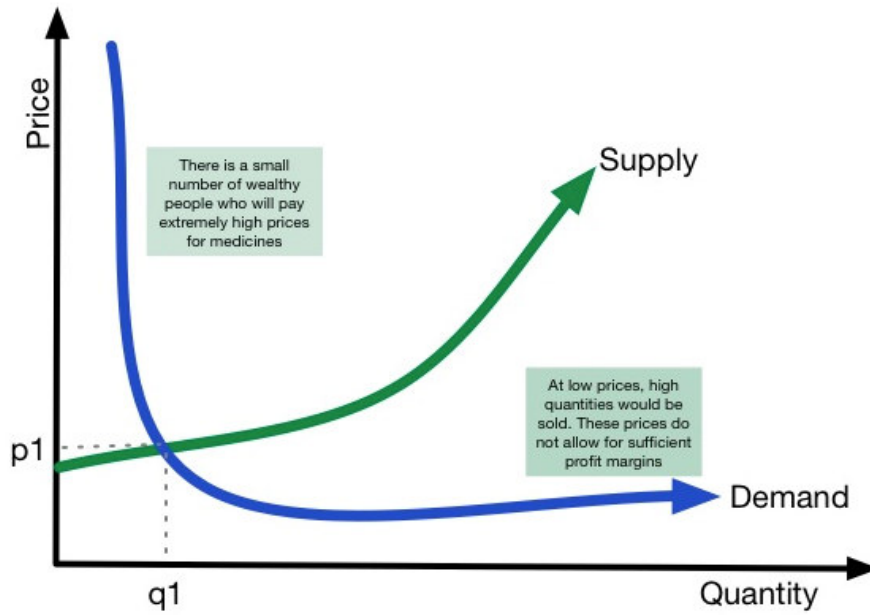


Figure 2.2. Market dynamics for drugs in low-income countries

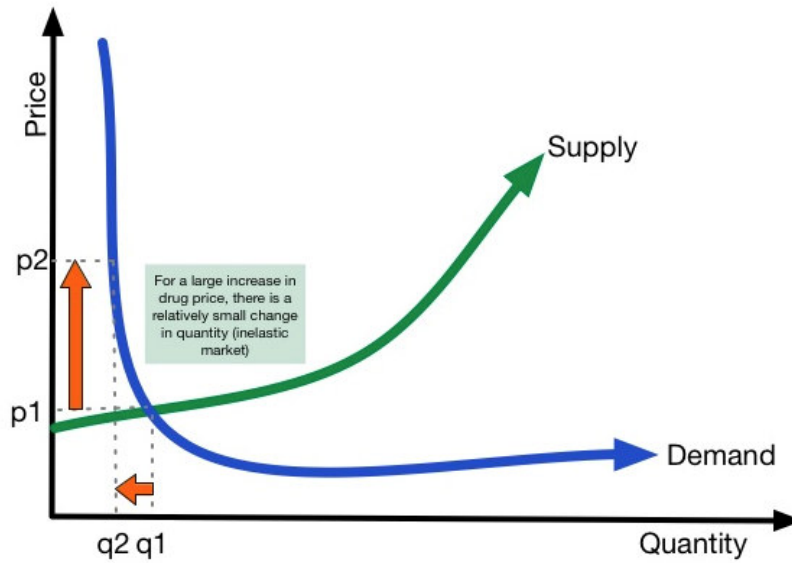


Figure 2.3.. Price elasticity for drugs in low-income countries

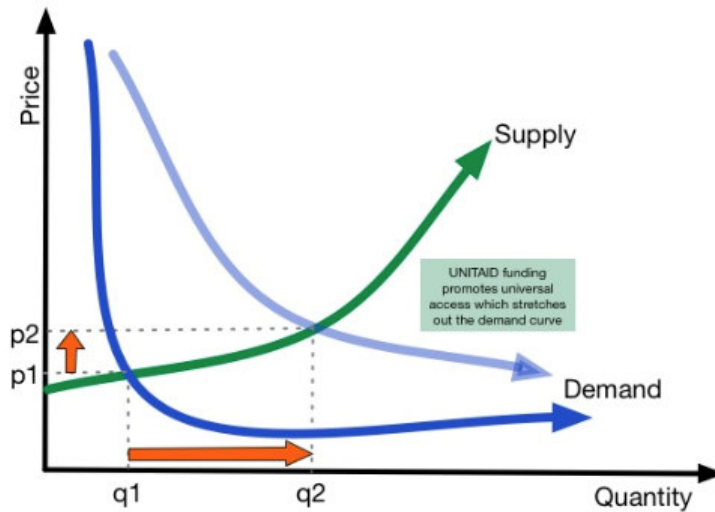


Figure 2.4. Changes in market dynamics with donor intervention

Various conditions need to be met in order for markets to work efficiently. In the absence of these conditions, markets are set to fail (that is, price fails to approximate value). These conditions include:

1. Many buyers
2. Many sellers
3. No barrier to entry for new suppliers
4. No barrier to exist for existing suppliers
5. Information efficiency
6. No “externalities” (costs and benefits not incurred by the participants in a given transaction)
7. No public goods (non-rival, non excludable goods)

In the case of the market for paediatric ARVs, the conditions above are not met and the possibility for market failure therefore exists. There are relatively few supply companies (especially in niche pharmaceutical areas like paediatric ARVs), there are few buyers (The Clinton Foundation using funding from UNITAID buys more than 80% of the global paediatric ARVs supply), there are significant barriers to entry into the market (the WTO TRIPS agreements ensures patent protection for at least 20 years), there is poor information efficiency (due to a lack of information systems allowing for demand forecasting in poor countries) and there are important social externalities associated with keeping children alive. These are just a few of

the factors that mitigate against traditional market forces being an adequate mechanism for the supply of paediatric ARVs. \

2.3 Theoretical Consideration 2: Stakeholder Power

Gardner and Rechlin (1986) describe how stakeholders can be mapped by considering their relative power against their relative levels of interest (Gardner & Rachlin 1986) - see figure 2.5 below.

Power / Interest Matrix (Gardner et al. (1986)

		Level of Interest	
		Low	High
Power	Low	A Minimal effort	B Keep informed
	High	C Keep satisfied	D Key players

Figure 2.5. Stakeholder power and interest

The application of the underlying theoretical considerations of this model can be thought of in the context of the pharmaceutical industry and their relative ‘power’ (capacity to influence and engage in the R&D of paediatric ARVs) and their level of interest in doing so (the extent to which they consider the market for these products to be an attractive area for investment).

Pearce and Robinson list groups of stakeholders including: shareholders, employees, customers, suppliers, governments, unions, competitors, local communities and the general public (Pearce 2008). However for the purposes of this research project, we will use Freemans definition of the stakeholder, “any group or individual who can affect or is affected by the achievement of the organization’s objective” (Freeman 2010a).

Winstanley et. al. proposed a model through which managers can understand where it is that stakeholders might exercise power (Winstanley et al. 1995). They argued that power can be applied in two distinct ways:

1. Critical power – the power to define the goals, aims and purpose of the organization
2. Operational power – the power to determine how the product or service offered by the company is provided by the allocation of a range of resources.

Agle et. al. propose a more recent model in which stakeholder behavior is grouped into various types, depending on the combination of three characteristics (Agle et al. 1999):

1. POWER of the stakeholder to influence the organization.
2. LEGITIMACY of the relationship and actions of the stakeholder with the organization in terms of desirability, properness or appropriateness.
3. URGENCY of the requirements being set for the organization by a stakeholder in terms of criticality and time-sensitivity for the stakeholder.

All three models are useful tools in considering the relative power of interested stakeholders and their respective objectives. Chapter 5 includes a “stakeholder map” and highlights the involvement of the state, the private sector and global health institutions, all of which have different levels of power and legitimacy when it comes to critical decisions that are made with regard to the nature and type of collaborative initiatives undertaken in the area of drug development.

2.4 Summary

Chapter 2 has explored some of the economic and social realities that R&D for paediatric ARVs exists within. Within the free market system that predominates, companies meet the demand for goods and services at a price and in quantities that are appropriate to their costs and need to generate a profit.

The supply and demand model can be used to understand the market for medicines in poor countries in general (which apply to paediatric ARVs). The intervention of multilateral donor agencies (like UNITAID) who provide financing for the procurement of drugs have the effect of straightening out the 'demand' curve and increasing access to medicines in poor countries. The importance of this model with respect to R&D for paediatric ARVs is revisited in chapter 6 (Conclusions and Recommendations).

A second theoretical consideration is stakeholder power. In the context of partnerships and collaborative initiatives, the relative power and interest of the various stakeholders will determine the nature and effectiveness of the partnership.

While market dynamics and stakeholder power are not themselves the subject of this investigation, they are however essential concepts that must be integrated into the analysis of the data collected in this study.

Chapter 3 Literature review

3.1 Introduction

The theoretical considerations underlying some of the key issues related to this study have been opened up in chapter 2. Chapter 2 has moreover, allowed the unraveling of much of the complexity relevant to the practical or business issues addressed by this research thus establishing a business case for the research.

The purpose of this literature review is to consider, with respect to the three stated objectives established in chapter 1 above, what work has already been done and what body of knowledge has already been established. By establishing such a baseline, the author has been able to make informed decisions as to what line of questioning to follow when interviewing the participants of the study.

While the primary data for this study has been collected through in-depth key informant interviews, the literature review should be considered to be an important part of the overall dataset and indeed a platform of knowledge upon which the final data analysis has taken place.

This literature review considers four key ideas:

1. Public health need for paediatric ARVs
2. Stakeholder interests in the area of paediatric ARV supply
3. Partnership logic between public and private entities
4. Stakeholder power

Search engines and online databases used for this study included:

1. EMBASE
2. CINAHL
3. The Cochrane library
4. MEDLINE

5. Google Scholar

The Boolean search terms entered into databases include:

(Public private partnerships OR partnerships for product development OR PPPs OR global health partnerships) AND (product development OR drug development OR R&D OR research and development OR pharmaceutical OR stakeholder interest AND underserved markets OR market failure OR drugs for neglected disease) AND (HIV OR Paediatric HIV OR Paediatric ARVs OR Pediatric ARVs OR ARVs)

Refining the list of potentially relevant manuscripts was done through a process illustrated in figure 3.1 below.

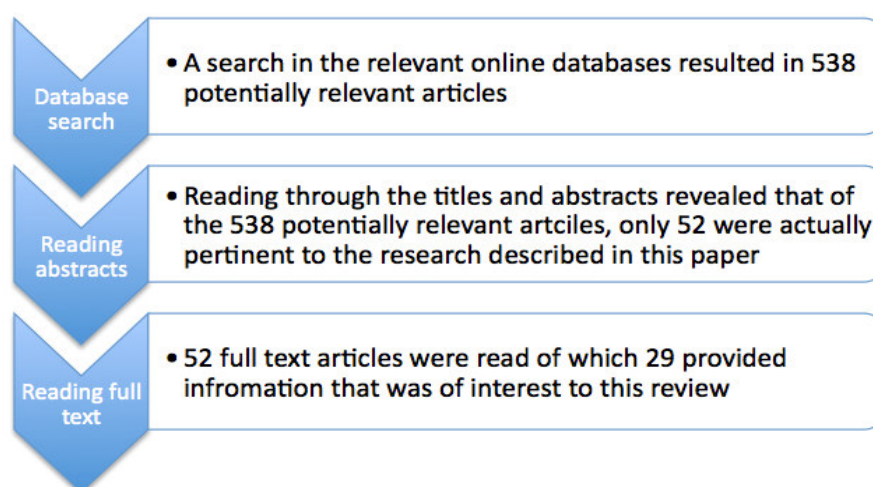


Figure 3.1. Literature review process

Each of the 29 papers was read with a view to extracting relevant information and understanding in the four areas of interest. Key ideas were extracted and then compiled under the headings of: public health need, stakeholder interest, partnership logic and stakeholder power.

The literature review produced the following results:

3.2 Public health needs

The clinical imperative to address the issue of developing formulations for children are highlighted by studies that show that when ARVs are used on HIV infected children:

- 73% survival at 24 months for children with <5% CD4¹ cells vs 98% in children with >5% CD4 cells (Fassinou et al. 2004)
- After 756 days on ARVs, 50% of children had undetectable viral loads² (Fassinou et al. 2004)
- The median CD4 cell% of children on ARVs rose from 3% to 21% at 72 weeks (Puthanakit et al. 2005)
- 75% of patients had HIV RNA³ levels of < 50 copies /ml at 72 weeks (Puthanakit et al. 2005)

In discussing the need for industry to engage more proactively with the public health needs in Africa, Scheffler (2005a) brings home the message that in 2001 the major items on the global R&D agenda included CNS disorders (26%) Cancer, Endocrine and Metabolic disease (22%) and cardiovascular (18%). Spending on research on developing an HIV vaccine accounted for less than 1% of global R&D (Scheffler & Pathania 2005a).

Dionisio (2006) points to fact that a major limitation that many Africa countries face in pharmaceutical production is lack of capacity and infrastructure in the manufacturing process required to produce quality drugs. He points out that in Africa, the generic pharmaceutical industry requires:

1. Increased availability of trained human resources for quality manufacturing
2. Greater depth of expertise in multilevel Standard Operating Procedures for quality manufacturing
3. Higher levels of quality manufacturing and analytical technologies

¹ CD4 cells are part of the immune system. A CD4 count is a measure of the patients ability to mount an immune response. AS the disease progresses, the CD4 count falls.

² Viral load is a measure of the actual number of HIV viruses that can be counted in a milliliter of blood. Like CD4 count, this is a measure of the progress of the disease. A higher viral load represents a poorer prognostic sign for the patient.

³ The HIV RNA gives an indication of the viral load in the patient.

4. Improved local sourcing of raw or semi-finished materials, with tariff barriers eliminated for importation
5. Enhanced capabilities for local chemistry synthesis procedures
6. Improved quality monitoring skills at National Drug Regulatory Authorities
7. Greater government incentives
8. Improved access to ample donor support

Dionisio et. al. goes on to highlight the fact that only one third of sub-Saharan African countries have capacities for secondary manufacturing. Very often when they do have capacities, they are not in full Good Manufacturing Practice (GMP) compliance (Dionisio et al. 2006). While this point represents a problem that needs to be addressed within the context of a wider discussion on economic development across multiple sectors (not just healthcare products), it is nevertheless of interest as national capacity in this area translates directly into increased access to essential medicines.

Factors that have lead to under investment in R&D for diseases in poor countries are listed by Wheeler and Berkley (2001a) and include:

1. Perceived and actual low market returns for these investments
2. Distribution challenges in poor countries
3. Lack of awareness / understanding of the public health needs in poor countries (Wheeler & Berkley 2001a)

The point made by Wheeler and Berkley should be seen as an extension of the problem highlighted by Dionisio et. al. in that national capacity in the area of drug development needs to be complemented by an ability to ensure that those drugs are effectively distributed within that country.

Expanding on the problem of access to medicines in poor countries Heywood (2002) lists the major barriers to access in Africa as:

1. Rising disease pandemics,
2. The high prices of patent-protected drugs,
3. Poverty,

4. Infrastructure and
5. Political will (Heywood 2002)

While the issue of manufacture and distribution of drugs is paramount to this inquiry, the fundamental problem of new drug development must be addressed. Pecoul (2004) points to three gaps in the R&D pipeline for medicines for underserved markets:

Discovery

Gap 1 – Basic research is published but preclinical research is not considered worthwhile

Predevelopment

Gap 2 – Validated candidate drugs don't enter the clinical development stage because of profit-based company choices

Development

Gap 3 – Drugs never reach the patent due to registration problems, lack of production, high prices or drugs poorly adapted to local conditions. Availability to patient (Pécoul 2004)

The importance of “access” to healthcare products must distinguish between “potential access” (the presence of healthcare) and “realized access” (the actual use of healthcare services) (R M Andersen 1995). Thind and Andersen (2003) state that potential access is a function of availability and accessibility; for example the rural urban differential and the time to reach a health facility (Thind & Ronald Andersen 2003)

3.3 Stakeholder interests

According to Freeman et. al. (2010b) Stakeholder Value Perspective the very purpose of a firm is to coordinate the various interests of the stakeholders (Freeman 2010b).

Exploring the idea of “stakeholder interest” Charls Handy (2002) makes reference to the ‘enlightened business’ that recognizes that it is possible to make money and do some good at the same time (Handy 2002). Goodpaster (1988) suggests that an organizations mission statement should be the

product of negotiation with the various concerns of stakeholders (Goodpaster 1988).

Importantly, for profit companies are not the only organizations that engage in R&D. Hale (2005) explores the concept of “nonprofit pharmaceutical companies” that have R&D capacity and are driven by public health needs and not financial remuneration per se (Hale et al. 2005). Added to this, non fiscal incentives for pharmaceutical companies to engage in R&D partnerships represent an additional mechanism through which R&D can take place. These incentives are listed by Wheeler and Berkley and include:

1. Access to knowledge
2. Access to platform technologies that allow for the development of other drugs
3. Competitive advantage
4. Access to markets (Wheeler & Berkley 2001b)

Examples of existing partnership are explored in the literature and include work done by Lim (2005) which shows that in Singapore’s health sector, the private sector was incentivized to engage in partnerships with the public sector by the prospect of being able to access international markets for healthcare (Lim 2005).

Initiative within the private sector that have altruistic as well as profit motives are looked at by authors such as Vian et. al. who published a study that looked at Pfizer’s Global Health Fellows programme that worked with health organizations in low income countries in an effort to improving staff performance with those organizations (Vian et al. n.d.). In this example, the public sector were seeking to improve human capacity while Pfizer categorized this as one of their ‘corporate philanthropy programmes. Of interest is the extent to which Pfizer was incentivized by altruism or, alternatively, the desire to make working for them more attractive (clearly the 72 members of staff that took part would have been interested in this opportunity).

In addressing the problem of the development of new paediatric ARVs it is important to consider similar work done in addressing problems in other disease areas. Njau et. al. (2009) conducted a study into public private partnerships in Tanzania that were aimed at malaria control. Their study found that the process was driven largely by stakeholders that had common vision and the involvement of senior politicians in the process (Njau et al. 2009).

3.4 Partnership logic

Global Health Partnerships are described by Buse and Harmer (2007) as:

“...collaborative relationships among pharmaceutical companies in partnership with UN-based organizations, developing country governments and public and private foundations to ensure efficient product development, healthcare delivery and technical support for implementation of national disease programmes” (Kent Buse & Harmer 2007)

Pointing to the fact that, partnerships with the private sector have emerged out of necessity, Nishtar (2004) shows that this necessity is a function of the failure of the public sector to provide adequate public health facilities on their own (Nishtar 2004).

Karki et. al. (2007) point to the dramatic effect that public private partnerships have had on TB control in Nepal. They point out that while PPP schemes had a low additional cost, the case notification rate was more than doubled (Karki et al. 2007)

Hypothetical options for collaboration between the pharmaceutical industry and the public sector are explored by Scheffler and Pathania (2005a) who argue that this represents an opportunity to increase the availability of drugs in the developing world. This addresses the need for the pharmaceutical industry to have their IP protected and to generate a profit and balance it with the human right to life and health (Scheffler & Pathania 2005b).

Reasons why pharmaceutical companies might take an interest in Global Health Partnership are listed by Scheffler:

1. In some cases they get to retain the property rights of new medicines (subject to their commitment to sell the product at marginal cost in developing countries)
2. Spin off benefits of the R&D done. New knowledge gleaned can be used in the development of other products
3. Companies gain an understanding of and access to new markets
4. Small biotech firms can get into the spotlight and gain visibility leading to more funding and potentially bigger orders
5. Project themselves as good corporate citizens (Scheffler & Pathania 2005a).

Wheeler and Berkley (2001b) describe the characteristics of Product Development Partnerships (a class of PPP) as:

1. Small and effective management teams that coordinate project selection and portfolio management, low overheads and operational flexibility
2. Disease specific focus
3. Funding from public and philanthropic sectors with in-kind contributions from the private sector through project partnerships
4. Funding of projects that have a commercial component to them as well as a well defined public health objective
5. Decision-making typically lies with partnership management who have retroactive accountability to the Board and other stakeholders. This allows for project initiation, termination and adjustment without complicated and cumbersome approval mechanisms
6. Clear recognition of Intellectual Property Rights (IPRs) (Wheeler & Berkley 2001b)

In a two part series, Buse and Walt (2000a) consider firstly the generic factors that have driven the emergency of public private partnerships in the global health arena (K Buse & Walt 2000a) and secondly whether or not shared goals can transcend conflicting values and mandates. The series

concludes that the current climate of goodwill between the public and private sectors offers an opportunity that should not be missed (K Buse & Walt 2000b).

A study into the cost savings associated with the building of hospitals through public private partnerships was published by McKee in an effort to consider the cost effectiveness of such endeavors (McKee et al. 2006). While cost is clearly an important issue in the public sector, McKee points to the fact that there is evidence that quality was compromised and that due to the complexity associated with these kinds of projects, it becomes increasingly difficult to 'future proof' them.

Other examples in the literature include that published by Lim (2005) which examines public private partnership in Singapore and shows how through partnerships an increase in flexibility has allowed Singapore to become a regional hub in terms of health care provision. (Lim 2005).

Krupp et. al. (2009) examine maternal mortality in India and compare and contrast various strategies that are being undertaken to address the human resource shortage that contributes significantly to the problem. They ask whether public private partnership should be scaled up instead of increasing public sector health systems (Krupp & Madhivanan 2009). They conclude that a combination of public sector enhancement and private sector involvement is appropriate.

3.5 Summary

The literature review starts by establishing the clinical effectiveness of ARVs for use in children. It goes on to highlight the dearth in investment into R&D for 'neglected tropical disease' in general and the need for developing countries to establish domestic R&D and production capabilities of their own.

Factors that are listed as contributory to the lack of R&D in this area include:

- 1) low returns on investment, 2) poor distribution channels in poor countries, 3) lack of awareness of the demand for these products.

The literature highlights the need for a common vision among stakeholders if partnerships are to be established to address the R&D pipeline. While companies are primarily driven by profit incentives, examples exist of companies engaging in partnerships out of a sense of corporate social responsibility and for other non-fiscal benefits include: 1) access to platform technologies, 2) competitive advantage through improved access to markets in poor countries 3) improved public relations.

The literature points to the fact that partnerships are needed because of a failure of public institutes to adequately provide healthcare facilities and medicines on their own. The logic of partnerships lies in the potential to balance the right to life with the possibility for companies to make a profit.

Shortfalls in Public Private Partnerships (PPPs) are described, in particular a concern with a problem of 'quality'. Where PPPs have been shown to be successful however, the literature states the importance of scaling these initiatives up.

The importance of PPPs in the health sector is emphasized and the establishment of new PPPs in the area is suggested.

Chapter 4 Research design and methods

4.1 Introduction

The preceding chapters have outlined the research objectives of interest, outlined some of the theoretical issues that underpin those objectives and explored the literature to establish a baseline of knowledge with respect to those objectives. This chapter considers the theoretical and practical aspects of the research methods employed to ensure that the research objectives stated in chapter 1 were met in a logical and repeatable way.

4.2 Study design

Cooper and Schindler (2008) define research design as

1. an activity,
2. based on a research question,
3. guides the selection of sources of data,
4. is a framework for specifying relationships between variables and
5. outlines procedures for every research activity. (Cooper and Schindler 2008).

The study design described below is based on the framework described by Cooper and Shindler (2008) and clearly delineates the type of study being undertaken, how it is that the data for the study was collected, the identified population of interest, the sample size and sampling process before going on to describe the method of analysis, limitation of the study and ethical considerations.

4.2.1 Study type:

Martins et. al (1996) describe qualitative research as the collection of data from a large number of people with the intention of projecting the results to a wider population (Martins et al. 1996). This is a weak definition of qualitative research in that it assumes that the investigation falls under the aegis of

‘social science’ and that the subjects are human. For the purposes of this study however, it is nevertheless appropriate.

Importantly qualitative research collects data that is not primarily numerical. A common misconception is that the analysis of qualitative data is never statistical. This is not necessarily true as following the coding of qualitative data, statistical analysis is often possible and appropriate. As is suggested by the word itself however, qualitative research attempts to unpack and understand qualities (and not magnitudes) associated with the subject of interest (Sandelowski 2000).

This study is a qualitative investigation drawing on data collected through a series of in depth interviews and complimented with information and understanding gathered through a narrative literature review of peer reviewed articles on the subject matter of interest and a review of key documents available on the WebPages of institutions of interest.

4.2.2 Data collection

“In-depth interviews: face to face conversation with the purpose of exploring issues or topics in detail. Does not use pre-set questions, but is shaped by a defined set of topics or issues” (Pope & Mays 1995)

Interviews were held in person or done over the phone/skype. All interviews were recorded and transcribed. Given the diversity of ideas and opinions that emerged, pre-coded questions were not used. A semi-structured interview allowed the interviewer to dig deep on issues that arose. A detailed description of the Interview Protocol is provided in Appendix 2 below.

Importantly, the preceding literature review allowed the author to build upon existing ideas and generate informed questions into the subject matter as the interviews proceeded.

4.2.3 Population of interest

The population of interest in any given study is the entire group about which the sample selected is expected to represent. Most studies do not examine the entire population but rather try to identify a representative sample that captures the important elements of the population (Sandelowski 2000).

In this study, the population of interest includes all decision makers that have experience in driving public / private cooperative initiatives in the area of drug development for diseases in underserved markets. These include representatives from the private sector (pharma / biotech), global health institutions (WHO, UNITAID and the Medicines Patent Pool) and clinical experts in the field.

4.2.4 Sampling process

A small focused sample has been chosen using a 'snow-ball' technique. A snow-ball technique involves starting with a small group of known and willing participants and using the interview process itself to identify further candidate participants. A letter sent to interviewees asking them to participate in the study has been included as Appendix 1 below.

Inclusion criteria included

1. Knowledge of the subject of interest
2. Experience at a senior management level

Exclusion criteria included:

1. Known conflicts of interest
2. Lack of willingness to participate in the study

4.2.5 Sample size

A sample of 12 participants has been used.

4.3 Analysis

4.3.1 Method for data coding and classification

Pope and Mays (1995) described the process of “content analysis” as one in which qualitative data is examined and grouped into themes, categories and attributed codes. The process of content analysis should be complimented by “constant comparison” which is an iterative method in which as a new idea/code/category is identified, it is then searched for throughout the entire data set. All instances are compared until no new categories can be identified (Pope & Mays 1995).

All of the interviews conducted in this study were recorded and then transcribed. The author then undertook to read through all of transcripts of the interviews and through the literature review and group the emerging ideas and concepts in an iterative fashion as described by Pope and May (1995). As the Interview Protocol (see Appendix 2) allowed for the interview process itself to collect information under the headings of the three study objectives, data fell naturally into categories consistent with those objectives and are described in the results section of this report under the relevant headings.

4.3.2 Study validity and reliability

Cook and Campbell (1979) define validity as the "best available approximation to the truth or falsity of a given inference, proposition or conclusion." (Cook & Campbell 1979). Pope and Mays (1995) describe validity as the extent to which measurements truly reflect the phenomenon under scrutiny (Pope & Mays 1995). A study's validity is a function of sound study design and investigator integrity. Pope and Mays (1995) describe reliability as the extent to which a study, if repeated will yield the same results every time (Pope & Mays 1995).

The authors has made every effort to conduct the research in a manner consistent with the described study design and to, where possible, eliminate sources of bias and/or error from the data collection and analytic process.

Ultimately, study validity rests heavily on the integrity of the investigator. In this case, the author has focused on engaging in an honest enquiry into the facts surrounding the study objective.

4.3.3 Triangulation

Cohen and Lawrence (2007) define triangulation as an "attempt to map out, or explain more fully, the richness and complexity of human behavior by studying it from more than one standpoint." (Cohen and Lawrence 2007). Bogdan and Biklen (2006) describe triangulation as a technique that allows for the validation of data through cross verification from more than two sources. They particularly advocate the use of more than two research methodology (Bogdan & Biklen 2006). Altrichter (1993) contend that triangulation "gives a more detailed and balanced picture of the situation." (Altrichter 1993). Denzin (2006) identifies four basic types of triangulation (data, investigator, theory and methodological triangulation) (Denzin 2006).

This study uses three methods of data collection, i.e. the literature review of peer reviewed articles, a review of the WebPages and institutional documents from organizations of interest and in-depth interviews. These three sets of data have been used to inform and understand each other and so build a more complete picture.

4.4 Limitations

The Hawthorne effect is the impact that the research process itself has on the data obtained from the subjects being interviewed (or observed). Knowledge of a study has the effect of changing people's behavior (Pope & Mays 1995) and may represent a source of bias.

Limitations that have been encountered in this study include:

- Due to time and resource constraints, a limited sample of stakeholders were interviewed.

- The sample used may not be fully representative of the population of interest in that a) the starting point for sample selection was thought identifying known (to the author) potential participants and b) the snow-ball technique has a tendency to select other 'like minded' participants.
- The interviewer might have had a set of expected conclusions or outcomes of the study that affect his analysis
- The full array of types of organizations that engage in public private partnerships were not evaluated
- Participant interviewees may have provided information that is consistent with their own agenda
- Interviewees were relying on their memories of events which may at times be poor
- The fact that the data collected was not categorized by predefined codes means that an element of bias could have creep in during the analysis phase.
- As mentioned above, the Hawthorne effect impacts on the way that interviewees respond to questions being asked.

4.5 Ethical considerations

Each participant has given their express permission for the information that has been provided to be included in this study. Each participant was sent a letter (see Appendix 1) that explained the nature of the study in advance of the interview process. As described in the Interview Protocol (see Appendix 2), participants were assured that particular statements would not be directly attributed to individual interviewees unless explicit permission to do so was granted.

The ethical considerations for this study were given considerable attention given the serious nature of the subject matter (medical / public health). As the results of the study have the potential to impact policies that affect the health of some of the world most vulnerable population groups, every effort was made to ensure that in both the data collection and in the analysis of the data,

nothing was done or said that might negatively impact on existing plans or mechanisms to develop paediatric ARVs.

4.6 Summary

This study is a qualitative investigation based upon a clearly defined set of objectives. The study draws on three sources of data, namely: a review of the peer reviewed literature; information taken from webpage and documents of key stakeholders; and key informant interviews with 12 experts.

The population from which the sample of 12 experts was taken is the set of individuals with special knowledge of the R&D pipeline for paediatric ARVs and knowledge and experience in the area of Public Private Partnerships. Sampling was done using the snow-ball sampling technique and the list of participants is described in the results section of this report. Interviewees were all sent a letter in advance of the study (see Appendix 1) explaining the nature and objectives of the study.

Data was collected by conducting semi-structured interviews that were recorded and then transcribed. An Interview Protocol is available as Appendix 2 below. This data analyses used the 'constant comparison' and 'content analysis' methods and triangulated against information gleaned from the literature review and information available on the WebPages of key stakeholders.

Limitations of the study include the "Howthorne" effect in which the participants responses are affected by the very fact that they are participants in a study and other potential sources of bias like interviewer bias. Other important limitations include the small sample size the lack of precoded questions, interviewer bias and the reliance on interviewees memories.

Chapter 5 Results and discussion

5.1 Introduction

Chapter 4 outlined the data collection and analytical process that was undertaken. Interview data analyses used the 'constant comparison' and 'content analysis' methods and was then triangulated with the literature review and information available on webpages of key stakeholders. Ideas that emerged were categorized and then summarized under the heading of public health need, stakeholder interests and partnership logic below.

To reiterate the research objectives: they include firstly, understanding and describing the public health need for R&D into paediatric ARVs; secondly understanding and describing the various stakeholders and their respective interests; and finally exploring and indentifying potential collaborative / partnership opportunities that can be employed to address the existing public health need while satisfying the various stakeholder interests at play.

5.2 Public health need (Objective 1)

In discussing the public health need with participants, the following categories emerged:

1. The clinical imperative
2. The moral imperative
3. The need for innovation
4. Product related problems
5. Market related problems
6. Public health systems related problems

5.2.1 The Clinical imperative

As highlighted in the literature review, treating children with ARVs is extremely effective in terms of increasing their quality and length of life. This fact was also highlighted by the clinical experts interviewed.

5.2.2 The moral impetus

Interviewees that work in the context of global public health initiatives made reference to the various commitments made by transnational agencies, multilateral institutions and individual governments. For details of these commitments, please see Appendix 3 below.

5.2.3 The need for innovation

Clinical experts interviewed highlighted the fact that for effective management of paediatric HIV/AIDS the major innovations that need to be either developed or made accessible in developing countries include:

1. Novel treatments with improved effectiveness (especially in the light of drug resistant strains of HIV)
2. Novel or augmented products that are suited to the developing countries environments (including heat stability, improved shelf life and decreased pill burden)
3. New formulations that include
 - a. Dose optimization
 - b. Liquid formulations for very young or very sick patients
 - c. Fixed dose combinations (FDCs) that improve adherence and contribute towards easier supply chain management

It was noted that most ARVs are developed in the context of servicing rich country markets. For this reason, the highest 'non-toxic' doses are generally used in the formulations. Because of the high profit margins used in rich countries, the cost of active ingredient in the drug represents a small contribution to the overall price of the product. This is not the case in poor countries as the reduced price often approximates the cost of the active ingredients. Lower dose formulations would therefore have a marked impact on the price and hence the availability of these products in Africa.

A particularly important type of product was highlighted by the clinical experts interviewed, that is Fixed Dose Combinations (FDCs) which are products that contain more than one active ingredient and allow patients to take just one pill instead of a few pills at a time.

5.2.4 Product related problems

Specific problems outlined by clinical experts that were interviewed with regards to existing products included:

1. D4t liquid formulation requires refrigeration and is therefore inappropriate in many high burden countries
2. 3TC is only indicated for children over 3 months of age
3. AZT has a low dose to volume ratio and is therefore needed in very high volumes in older children in order to get adequate doses
4. NVP cannot be used in conjunction with rifampicin for children with TB due to drug-drug interactions that results in low blood concentration of NVP
5. There is limited data available on the use of EFV in children less than 3 years of age
6. 2nd line treatment (used for treating children who have developed resistance to the 1st line treatment) is problematic as they need cold storage and there is no generic equivalents available.

Given the fact that 40% of children requiring ARVs are less than 18 months, there is a need for the development of FDC for oral suspensions and solutions. Lack of paediatric labeling (particularly for infants) also represents a significant problem. In 2005, only 12 of the 20 ARVs were labeled for paediatric use and just 7 for children under 2. Lack of uniformity of distribution of active ingredients in adult pills means that breaking pills in half for paediatric use does not ensure accurate dosing in children.

5.2.5 Market related problems

Experts from industry highlighted the various market and regulatory related issues with respect to addressing the public health needs that exist in poor countries. These included:

1. The demand for paediatric ARVs is likely to dwindle with time, especially in the light of the WHO, UNAIDS and UNICEF's commitment to "virtual elimination" of Mother to Child Transmission (MTCT) by 2015. Market incentives for pharmaceutical companies to invest in developing these products is therefore limited.

2. Bioequivalence and pharmacokinetic studies in children are difficult and do not fall within the usual capabilities of generic companies (who are the most likely supply source of these products). Where FDCs for adults are changes to be appropriate for children, clinical trials need to be repeated to demonstrate efficacy in children.
3. Children are growing and so need different doses over time. This means that the “product” (any particular formulation) does not have a long-term “consumer” for “continued use”.

Almost all of the participants made reference to the fact that typical market incentives have not been adequate to drive R&D in the area of paediatric ARVs. Whether directly or indirectly, all of the interviewees talked about ‘market failure’.

Typically, markets work when the price and quantity sold/consumed of a product is a function of the intersection of supply and demand - or marginal cost and marginal benefit (see figure 2.1 above). For this mechanism to work however, a particular set of criteria need to be met: lots of buyers, lots of sellers, information efficiency, low barrier to entry into the market, low barriers to exit from the market, no externalities (costs or benefits incurred by a party not engaged in the commercial interaction), no public goods (non rival, non excludable goods).

For many of these criteria, interviewees talked about reasons why they didn’t apply in this market. Patent protection provides a deliberate barrier to entry for new (small) companies, as does the complex regulatory environment associated with drug licensing. There are also very few buyers and sellers in the market for paediatric ARVs (as large agencies tend to do procurement on behalf a number of countries at once). Also, in the case of healthcare, both positive externalities and public goods are desirable. Appendix 5 below draws upon the literature review to lists some of the many reasons why there is an inherent ‘demand / supply’ mismatch in this area of the economy.

However, even if markets could be used to set “price and quantity” for HIV commodities in poor countries, the capital budgeting process (described above) make engaging in R&D for these projects unattractive for many commercially driven entities.

The most powerful mechanism that can be used to mitigate failure in the HIV commodity market is the establishment of partnerships that share costs, risks and benefits. As well as cost sharing and price concessions, other outcomes of these partnerships were talked about by participants, including the need for:

1. Early engagement with supply chain and ensure transparency of business processes
2. Clearly define requirements (demand) for supply side to respond to
3. High level of flexibility with regards to commercial / contracting options
4. Highly visible commitment to procurement
5. High burden countries must evaluate local barriers to entry into their markets
6. Governments must make use of flexibility in trade legislation to facilitate licensing
7. Early submission of dossiers to WHO prequalification scheme
8. Alignment of activities of buyers, suppliers and users
9. Optimization of supply chain management to decrease inventory and operation costs and ensure quality assurance

Participants highlighted the fact that without reliable demand forecasting and associated efficient global supply chain management, these markets will continue to be unattractive to commercial interests. Barriers to the global supply chain include:

1. Uncertain political stability
2. Lack of infrastructure
3. Lack of critical market mass in certain countries
4. High transaction costs due to slow adoption of e-business
5. Poor information sharing and accurate demand forecasting

6. Poor electron linkages to communicate and release supply requests and reports

5.2.6 Public health systems related problems

Policy experts interviewed made reference to the problems associated with scaling up paediatric HIV treatment in poor countries:

1. Limited capacity in poor countries to scale up treatment programmes
2. Lack of focus on HIV positive children by donor agencies and governments
3. High cost of paediatric ARVs (50-90% higher than adult versions of branded products)

5.3 Stakeholder interests (Objective 2)

In discussing the issue of paediatric ARVs with interviewees, the participants were specifically asked to list important stakeholders that drive R&D for new products. Following reflection on the data, the following stakeholder map was drawn up.

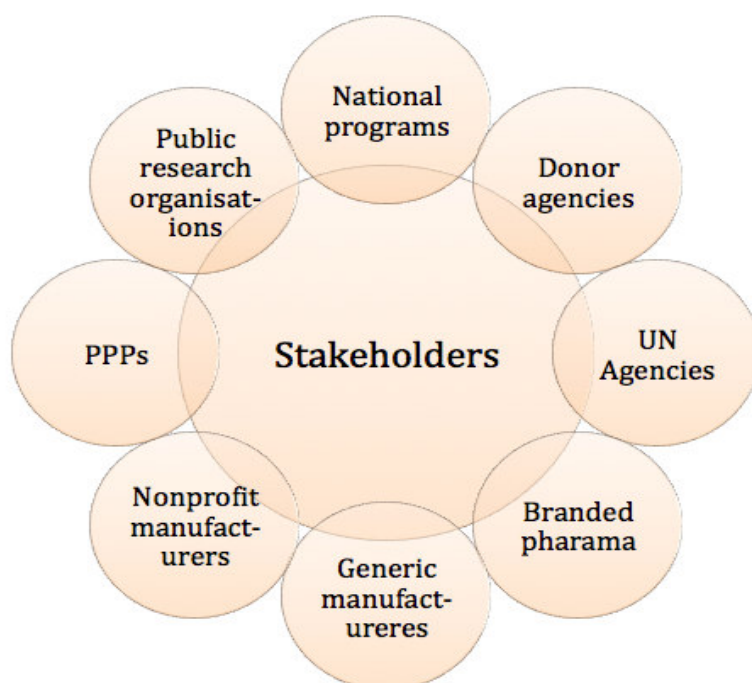


Figure 5.1. Stakeholder map for R&D of HIV drugs

Participants were asked to describe the various interests that the stakeholders identified might have and to discuss the decision making process that is undertaken when considering the R&D for paediatric ARVs.

5.3.1 Branded companies

Branded companies typically engage in R&D for new products that are usually intended for rich country markets. All interviewees agreed that branded pharmaceutical companies are arguable the easiest to understand in that they have a very clear mandate that is to maximize shareholder value.

However as emphasized by those from the public sector, there are numerous non-fiscal benefits that can be attained by private sector companies engaged in the R&D for paediatric ARVs that include:

1. Increased access to markets in poor countries for other products
2. Improved public relations
3. Access to new “platform” technology
4. Risk sharing with public entities

Branded and generic companies are likely to make decisions as to whether or not to engage in R&D for these products through a capital budgeting process (described below).

5.3.2 Generic companies

Generic companies typically market “off patent” products and so circumvent the high R&D costs associated with producing novel products. They are therefore often far better suited to engage markets in poor countries.

Participants from pharmaceutical industry stated that generic companies are driven by the same set of decision-making processes as branded companies but are however constrained by the fact that they typically do not have in-house research capabilities which are needed even for off patent products that are being reformulated and then licensed for paediatric use (as most ARVs are developed for adult use initially)

5.3.3 Non-profit pharmaceutical companies

One participant gave an anecdotal example of the Institute for One World Health that is a nonprofit pharmaceutical company that has

1. In-house R&D capacity
2. Tackles a wide variety of neglected diseases and select the best development opportunities available in each
3. Is limited in the modality of treatment (drugs, vaccines and diagnostics can be developed as needed)

Nonprofit pharmaceutical companies often adopt post-discovery compounds that have substantial safety and efficacy data but that have not been commercially developed by Branded companies (who either license or donate the intellectual property (IP)).

It was pointed out that these companies represent an appropriate vehicle for the development of products from active ingredients that have proven efficacy but that have been abandoned by Branded companies due to a lack of anticipated profitability.

5.3.4 Product Development Partnerships (PDPs)

“Product development partnerships (PDPs) are a class of public–private partnerships that focus on pharmaceutical product development for diseases of the developing world. These include preventive medicines such as vaccines and microbicides, as well as treatments for otherwise neglected diseases. PDPs were first created in the 1990s to unite the public sector's commitment to international public goods for health with industry's intellectual property, expertise in product development, and marketing” (for a list of PDPs, see Appendix 4 below).

The literature review highlighted important characteristics of PDPs that include the facts that they:

1. Have small and effective management teams that coordinate project selection and portfolio management, low overheads and operational flexibility

2. Disease specific focus
3. Funding from public and philanthropic sectors with in-kind contributions from the private sector through project partnerships
4. Funding of projects that have a commercial component to them as well as a well defined public health objective
5. Decision-making typically lies with partnership management who have retroactive accountability to the Board and other stakeholders. This allows for project initiation, termination and adjustment without complicated and cumbersome approval mechanisms
6. Clear recognition of Intellectual Property Rights (IPRs)

5.3.5 Social Venture Capital

Interviews with participants lead to in-depth discussion on 'social venture capital' initiatives, many of which represent Public Private Partnership and are discussed in more detail in the section on 'partnership logic' below.

Examples of Social Venture Capital (SVC) initiatives like International AIDS Vaccine Initiative (IAVI), the Medicines for Malaria Venture (MMV) and the Global Alliance for TB Drug Development (Global Alliance) were used as examples in discussion. Participants highlighted the fact that these initiatives finance projects in much the same way that a regular Venture Capital (VC) or Private Equity (PE) firm might, however, instead of requiring an equity share of the company, SVC initiatives negotiate obligations on the part of the companies that have strategic public health importance in developing countries. Generally these initiatives were considered by participants to be successful in terms of achieving their goals and were considered to be an important option for the future development of paediatric ARVs as they directly addressed the problem of failed 'profit' incentives for underserved markets.

These venture were also referred to as Partnerships for Product Development (PPDs) and specific areas of success were described with regards to other areas of product development, in particular TB, Malaria and HIV vaccine. A list of successful PPDs was extracted from interview data and then

complemented with examples found by searching the internet and revisiting the literature review performed (see Appendix 4 below).

5.3.6 National programmes

National HIV programmes within high-burden countries were identified as critical stakeholders for the development of paediatric ARVs. National programmes represent the interface between on the ground “need” and real market level “demand” as most HIV products are procured at this level. Two characteristic of HIV products were highlighted as important to national programmes, i.e. price and suitability (drugs for example that can be stored and transported at room temperature for areas that do not have ‘cold-chain’ capabilities). In terms of price, it was noted that tremendous efforts have been made by multilateral donor agencies like UNITAID and CHAI to impact the market dynamics and negotiate lower prices from both Branded and generic companies.

It was also noted that an national programmes needed to ensure more robust ‘demand forecasting’ (which will require more sophisticated health information systems) in order to make these markets more attractive to companies investing in R&D for paediatric ARVs.

5.3.7 Multilateral donor agencies

Interviews with senior management at UNITAID helped clarify their involvement in the R&D process. UNITAID is mandated to:

1. Impact market dynamic for HIV, TB and malaria products to achieve lower prices
2. Impact public health by increasing access to medicines.

UNITAID currently works with partners (like UNICEF and the Clinton Foundation) by financing the bulk procurement of products in the hope that these partners can negotiate lower prices through increased buying power.

Alternative strategies were talked about that included shifting the ‘supply curve’ to the right (see figures 6.1) by increasing competitiveness in the

market and ensuring substitute products. This could be achieved by partnering with private sector companies to facilitate R&D through either risk sharing arrangements or providing Advanced Market Commitments (AMCs) for products that are currently in the R&D pipeline.

5.3.8 The Medicines Patent Pool

The Medicines Patent Pool (MPP) represents a new innovation in the area of facilitating access to medicines. Since the establishment of the World Trade Organization (WTO) and the subsequent TRIPS agreement that governs Intellectual Property Rights, in-patent drugs have been made accessible to those living in poor countries through either 'compulsory licensing' (a provision within the TRIPS agreement that allows national governments to license products that are under patent in the face of a national health emergency) and voluntary licensing agreements with Branded companies. While this process has been effective in some countries, it represents prohibitive administrative burden on some poor countries that do not have the capacity to engage in these international legal proceedings for multiple drugs.

The Medicines Patent Pool is a facility that allows participant companies to allow IPRs for lifesaving drugs to be 'pooled' in one facility that can be accessed by multiple countries without each of them needing to enter into negotiations with each company individually.

In interviews with senior management at the MPP the importance of this facility in the context of R&D for paediatric ARVs was discussed. They highlighted the fact that new products are typically developed for rich country markets and that for these products to be made available in poor countries while under patent the regulatory issues that govern IPR need to be addressed in the most efficient way possible. They emphasize that R&D without facilitating access is largely a waste of time (from a public health perspective).

5.3.9 Private sector Capital Budgeting

In talking with representatives from the private sector, the importance of capital budgeting in the decision making process for companies was highlighted. Interestingly, it was felt that the public sector did not understand and did not engage with this process and that this represented a missed opportunity in terms of setting up meaningful collaborative and partnership initiatives between the public and private sector.

Participants discussed the fact that the monetary costs associated with investing in R&D for HIV drugs are weighed against anticipated returns. Companies typically use capital budgeting methods like determining the Net Present Value (NPV) or the Internal Rate of Return to compare alternative investment opportunities and so make decisions as to the most optimal use of capital.

The NPV is the current cumulative value of all future cash flows from a project, adjusted by a discount rate that is determined by the company. In the context of investing in drugs for developing countries, this 'discount rate' becomes particularly important. While companies typically use the Weighted Average Cost of Capital (WACC) that applies to the entire firm to discount future cash flows, the firm may choose a higher rate for projects that represent a higher risk than is typical for that firm's activity. It is likely that pharmaceutical companies adjust their discount rate up when considering projects whose market is chiefly in developing countries where the market place is poorly characterized, demand forecasting is weak and political stability is uncertain.

The IRR represents the interest rate at which the NPV of an investment would be zero. If the projects IRR exceeds the cost of capital, then the project may represent a desirable investment (depending of course on the IRR achievable via alternative uses of the same capital). Being a "rate", the IRR is an indication of investment yield and not magnitude (as is the case with NPV). This fact is important in the context of investing in HIV related products as the sheer magnitude of revenues from alternative investment for products

servicing rich countries would mostly dwarf those achievable from HIV products specifically made for poor countries.

5.4 Partnership logic (Objective 3)

By considering the public health needs for new paediatric ARVs and the various interests of the respective stakeholders above, participants were asked about possible overlapping interests and mechanisms that can be (or have been) used to ensure a 'win-win' scenario in the area of R&D for these products.

Buse and Harmer (2007) describe Global Health PPPs as collaborative relationships among pharmaceutical companies in partnership with UN-based organizations, developing country governments and public and private foundations to ensure efficient product development, healthcare delivery and technical support for implementation of national disease programmes (Kent Buse & Harmer 2007).

5.4.1 Public Private Partnerships

Many of the participants interviewed either worked within an existing PPP or had a special interest in PPPs in the area of drug development. Much of the discussion revolved around the past successes and failures of PPPs in drug development.

Partnerships are a mechanism through which many of the costs and risks (as well as the benefits) of engaging this market can be shared by the public and private sector.

Social venture capital, donor agencies or governments are often prepared to engage directly with pharmaceutical companies and assume some of the up front financial burden associated with R&D for products that have strategic public health importance in exchange for price commitments or assurances that certain population groups will be serviced.

5.4.2 Technology Transfer

Lack of national capacity to domestically develop and produce drugs in poor countries was mentioned by a number of participants interviewed. Currently only 1/3 of sub-Saharan African countries have capacities for secondary manufacturing. Very often when they do have capacities, they are not in full GMPs (Dionisio et al. 2006). Important requirements in Africa alluded to include:

1. Increased availability of trained human resources for quality manufacturing
2. Greater depth of expertise in multilevel Standard Operating Procedures for quality manufacturing
3. Higher levels of quality manufacturing and analytical technologies
4. Improved local sourcing of raw or semi finished materials, with tariff barriers eliminated for importation
5. Enhanced capabilities for local chemistry synthesis procedures
6. Improved quality monitoring skills at National Drug Regulatory Authorities
7. Greater government incentives
8. Improved access to ample donor support

Various UN resolutions, ratified by member states affirm a strong commitment by developed countries to promote and incentivize the transfer of technologies (particularly pharmaceutical) to developing countries so as to enable domestic production capabilities and so improve local access to life saving medications. See Appendix 6 for details of these resolutions.

Effective technology transfer would:

1. Improve national pharmaceutical policies
2. Diminish the supply of and demand for counterfeit drugs. Foster scientific capacity
3. Exert a positive impact on efforts to promote value added manufacturing activities
4. Increase employment and education levels (see Appendix 7 for examples of technology transfer project).

5.4.3 Incentives

Participants were specifically asked about mechanisms and incentives that can be (and have been) used to encourage R&D for products in underserved markets. Responses included reference to:

- Social venture capital arrangements (described above)
- Advanced market commitments (whereby donor agencies promise to buy a product in the event that it is developed)
- Health impact funds (a theoretical mechanism whereby the private sector would be paid for actual changes in health outcomes in a given population)
- Reward mechanisms (whereby R&D efforts would be rewarded regardless of their success)
- Fiscal and tax incentives

5.5 Discussion

Interviewees pointed firstly to the clinical effectiveness of ARVs when used in children and the fact that the life expectancy of children with HIV can be extended into adulthood. Various UN and donor agencies have subscribed to the 'moral impetus' to make ARVs available for children in poor countries (summarized in Appendix 3). While the ethical case for ensuring that children in the most vulnerable population groups be afforded life saving drugs is beyond the scope of this research, it is clear from the consensus within multilateral agencies (like the United Nations and World Health Organization) to which almost all nations subscribe, that if we are able to, we should do everything within our power to provide these children with treatment.

The public health needs were categorized in this study under three headings: 1) product related needs, 2) market related needs and 3) health systems related needs. Participants described the need for novel paediatric ARVs due to the emergency of HIV strains that are resistant to current drugs regimes. They also described the need for products that are appropriate to the context of low income countries like the need for heat stable formulations that don't

need transport refrigeration, low dose formulations that would be cheaper and Fixed Dose Combinations that would make transport and storage of products easier as well as decrease the pill burden for those taking the medicines. Liquid formulations and better tasting medicines for very young children was also highlighted as an important product related need.

Having established the public health needs and the existence of a demand for paediatric ARVs, the participants in this study went on to discuss some of the reasons that current market mechanisms are failing to meet that need.

Market related problems identified included a diminishing demand for paediatric ARVs, regulatory barriers and the fact that children (the end consumer) are growing and therefore need different products at different stages of their lives and so are not a 'fixed market'. Market failure in the area of paediatric ARVs was discussed and the need for partnerships and collaborative initiatives to address this failure was highlighted. A list of reasons for the failure of market mechanisms in this area is summarized in Appendix 5 below. The importance of understanding the changing market demand for paediatric ARVs in the context of normative economic theory (described in Chapter 2) cannot be over emphasized. The price and quantity of ARVs used is a function of the intersection of supply and demand. The normative economic models described in chapter 2 suggest that the problem can be address by shifting the supply curve to the right by decreasing the marginal cost of production. This principle underpins the rational for engaging in innovative partnerships in which cost sharing enables this shift.

It is essential that the interest of the various stakeholders (in both the public and private sector) be understood if partnerships are to be established to address the problem of R&D for paediatric ARVs. The data collected provides us with a detailed synopsis of these stakeholders and highlights some of the more pertinent incentives that drive these stakeholders. The various stakeholders were defined and included in a simple 'stakeholder map' (figure 5.1). Each of the stakeholders and their respective interests were considered individually.

Branded pharmaceutical companies are driven primarily by profit incentives and decisions about investment opportunities are subject to a capital budgeting process (like NPV or IRR). It was however pointed out that Branded companies are also influenced by non-fiscal incentives including: 1) corporate social responsibility, 2) access to new markets, 3) access to new platform technologies, 4) tax concessions, and 5) improved public relations.

Generic companies typically manufacture off-patent medicines and so circumvent the high costs associated with R&D of novel products. They do however engage in the development of new formulations of old drugs (identified as an important public health need) and so represent an important set of players in this area. Generic companies however often lack the capabilities needed to engage the complex regulatory environment needed to register new products.

There is a subset of pharmaceutical companies that are nonprofit and work with a strictly public health agenda. These include companies that do both primary research into novel products and development of new formulations of existing products. They also often enter into licensing agreements with Branded companies that allow them to access the Intellectual Property (IP) of products that Branded companies have chosen not to develop for low income countries.

Partnerships for Product Development (PDPs) - a subset of PPPs - have been shown to be extremely effective in developing products for TB and malaria. The partnership is typically between a pharmaceutical company and a multilateral donor (like the Gates foundation) or a national government. When donor agencies engage in risk / cost sharing with the private sector (often in the context of a Social Venture Capital initiative) they usually provide finance or a procurement commitment in exchange for guaranteed price concessions in areas of strategic public health importance.

Other structures like the Medicines Patent Pool (MPP) and the WHO Prequalification Initiative have been put in place to ensure that Intellectual

Property Rights can be easily accessed by low income countries and that regulatory hurdles can be easily overcome respectively.

The importance of engaging with the capital budgeting process of the private sector was highlighted. As companies take 'cost of capital' into account when determining an interest rate against which future revenue is discounted (when calculating the NPV or IRR), it is in the interest of public institutions to facilitate a decreased cost of capital for these projects.

The importance of partnerships in addressing both the public health needs and the stakeholder interests was emphasized by all of the study participants. As well as providing incentives to develop new products, these partnerships have other functions that include: improved demand forecasting, increased transparency, higher levels of commitment to procurement, improved engagement with the regulatory systems needed to register new products and improved supply chain management within countries.

Partnerships are also an effective way to ensure 'technology transfer' from rich countries to poorer countries. Appendix 6 lists the various commitments made by UN agencies to increase technology transfer and Appendix 7 lists examples of successful technology transfer. In addition to increasing the technical capabilities in terms of drug development and production within less developed countries, technology transfer also helps improve: 1) human resource capabilities, 2) standard operating procedures, 3) quality of products produced, and 4) supply chain management.

5.6 Summary

This chapter reports and reflects on the data collected in this study. The analysis of the data enabled well defined categories of information to be established and provided a platform for discussion that connected the data collected to the normative economic and business theory described and literature review described above.

The chapter starts by establishing both the clinical effectiveness of ARVs in terms increasing the life expectancy of children with HIV and the moral impetus to ensure access to these treatments that has been embraced by the international community at large.

Having established the need for R&D in the area of paediatric ARVs, the study participants described the market related issues that impinge on the development of these products. Declining demand, prohibitive regulatory constraints, poor local supply chain management, weak demand forecasting and a lack of perceived returns on investment into R&D were the important issues cited.

Participants were asked to identify the relevant stakeholders in the area of paediatric ARVs. A stakeholder map was drawn up that included: national health programmes, donor agencies, UN agencies, branded pharmaceutical companies, generic pharmaceutical companies, non profit manufactures, public private partnerships and public research organizations. The chapter describes each of these stakeholders and explores their respective interests and incentives so as to identify possible collaboration opportunities. Importantly, participants in the study highlighted the issue of capital budgeting and the decision making process that companies engage in when deciding between various investment opportunities. The importance of cost of capital was talked about and the lack of engagement by multilateral donor agencies in this area was pointed out.

The role of existing public private partnerships and the mechanisms at play in terms of cost sharing were described as well the impact of technology transfer from developed to developing countries as mechanisms that can be (and have been) used to combat neglected diseases.

The data collected, while addressing a number of issues, had at its core the theme of 'incentives'. In order to engage in R&D for paediatric ARVs, the private sector needs to be provided with the right incentives that include cost sharing, market commitments and non-fiscal incentives like IP protection and

access to platform technologies. The public sector by contrast need assurances that certain vulnerable populations will have access to the results of this kind of R&D and that prices for these populations will not be prohibitive. A number of innovative partnership / collaborative possibilities were described including:

- Social venture capital arrangements
- Advanced market commitments (whereby donor agencies promise to buy a product in the even that it is developed)
- Health impact funds (a theoretical mechanism whereby the private sector would be paid for actual changes in health outcomes in a given population)
- Reward mechanisms (whereby R&D efforts would be rewarded regardless of their success)
- Fiscal and tax incentives

Chapter 5 goes on to discuss these results and make the connections between the data collected and the normative economic models described in chapter 2 and information gathered in the literature review. The discussion laid out in chapter five provides a platform upon which the conclusions and recommendations presented in chapter 6 below are based.

Chapter 6 Conclusions and recommendations

6.1 Introduction

Chapter 5 above presents the finding of the research conducted. Following reflection on the findings, this chapter presents conclusions that can be drawn and then goes on to make specific recommendations.

6.2 Conclusions

6.2.1 Public health need

The need for new paediatric ARVs and more appropriate formulations of existing ARVs is apparent. Both the clinical and moral imperative for such innovations is universally accepted and the specific characteristic of needed products have been clearly delineated. Public health need however gets translated into market demand at a national health programme level as governments (often through multilateral agencies like UNICEF) do the bulk of the procurement of these products.

Market incentives for industry to engage in the R&D for new paediatric products is limited and this problem is compounded by prohibitive regulatory constraints that need to be overcome in order for these products to be made available and hence meet the needs that exist at a national level. With current public health interventions aiming at the elimination of mother to child transmission of HIV, the market for paediatric ARVs is set to become significantly smaller over the next decade. This represents an additional disincentive to develop new products in this area. The market impact of changes in demand for new products is discussed in more detail in the section on 'market dynamics' below.

6.2.2 Stakeholder incentives

While multiple stakeholders have been identified as important for the development of new products, these can broadly be classified in those that are part of the private and those that are part of the public sector. Private sector companies (including branded pharmaceutical companies, biotech

companies and generics companies) each play a role in R&D and are chiefly driven by the need to maximize shareholder value.

Branded companies typically develop products for rich countries but efforts are afoot (through initiatives like the Medicines Patent Pool) to ensure that despite existing patent protection, these products become available in poor countries too.

Some products however need to be specifically developed for poor country markets (like low dose and heat stable formulations). Initiatives like Product Development Partnerships and Social Venture Capital projects have been specifically set up with a view to addressing these needs by establishing risk sharing partnerships with the private sector. The mechanisms that underpin these partnership is discussed in the 'partnership logic' section below.

Government programmes and multilateral donor agencies (like UNITAID) are specifically geared up to engaging with the private sector to ensure lower prices of existing products and incentives to develop new products.

6.2.3 Partnership logic

Markets failure in the area of paediatric ARVs exists for a number of reasons, not least of which are high barriers to entry and a lack of a competitive environment. This is compounded by a lack in market incentives to engage in this area.

Lessons learned from experience in similar markets (for TB, malaria and HIV vaccines) show that Product Development Partnerships represent a viable alternative to usual market mechanisms. These partnerships usually involve a donor agency, government or Social Venture Capital initiative assuming part of the financial risk associated with R&D or providing incentives through Advanced Market Commitments for new products. In exchange, industry typically makes pricing concessions for the products in areas of strategic public health interest.

By providing incentives, sharing risk and more clearly characterizing the market (through more rigorous demand forecasting), it is likely that capital budgeting process undertaken by industry when examining these investment opportunities will assume a lower 'cost of capital' (or discount factor when calculating the NPV) and thus make developing these projects more attractive to them.

A multilateral donor agency like UNITAID is well placed to provide funds for initiatives of this nature as they have an explicit mandate to impact market dynamics for products used to treat HIV, TB and malaria.

6.2.4 Market dynamics

Normative economic theory suggests that the price / quantity equilibrium in the market is a function of the intersection of supply and demand. This model can be used to help us understand what might happen with changes in R&D investment into paediatric ARVs.

Strategic investment in new products would have the effect of creating substitutes for existing products and an increase in competitiveness in the marketplace that would in turn cause a 'right shift' in the supply curve in the market. Figure 6.1 below illustrates how, as the supply curve (marginal cost of production) is shifted to the right, the new equilibrium price / quantity is such that the market price is lower and the quantity consumed in the market is higher. From a public health perspective, this is a double win.

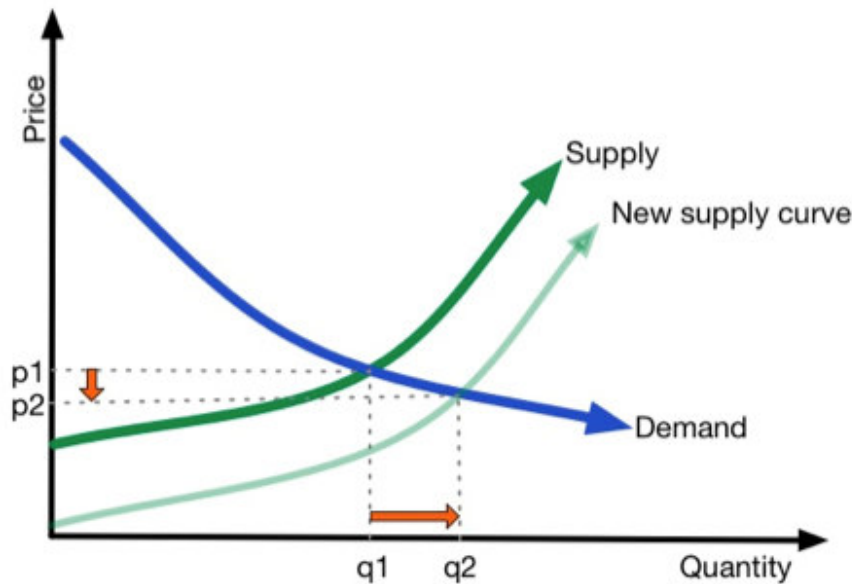


Figure 6.1. Shift in the supply curve

6.3 Recommendations

This issue of investment in R&D for paediatric ARVs is important and represents an opportunity to save the lives of millions of children in poor countries. This report approaches the problem from a business science perspective and considers the market place from a demand and supply perspective.

By understanding the need for paediatric ARVs and by delineating the interests of the various stakeholders that are involved with R&D, the report highlights the various complexities and barriers associated with the development of new products, not least of which is the poor financial incentives that exist for industry to engage in the development of these products.

It is clear however, that possibilities for partnerships that address incentives and impact on the private sectors capital budgeting process exist. By making efforts to more clearly define the market through enhanced demand forecasting and by providing risk sharing opportunities with the public sector, this market can be made more attractive to drug developing organizations.

Similar ventures have proven successful with respect to products for TB and malaria.

UNITAID is an example of a donor agency with a mandate to impact market dynamics for HIV products however its current strategy is confined to negotiating lower prices through bulk purchasing of drugs. This report illustrates that other mechanisms could be used by UNITAID to encourage R&D for paediatric ARVs illustrated in figure 6.2 below.

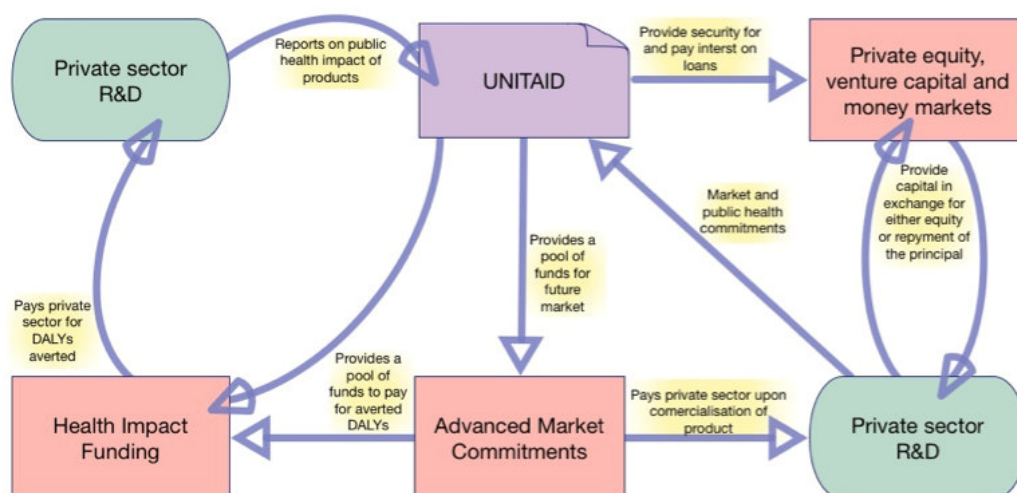


Figure 6.2. Possible financing mechanisms

By providing funds as either an Advanced Market Commitment or Health Impact Fund, UNITAID could ensure that the market for these products is more attractive to industry. Furthermore, UNITAID could work directly with existing money markets (like venture capital or private equity companies) and provide security for investment in R&D for paediatric ARVs.

Finally, UNITAID and other donor agencies should consider significant investment in health information systems in developing countries so as to improve demand forecasting and thus market characterization. By doing this, the return on investment in R&D for paediatric ARVs would be seen as a less risky venture for the private sector.

6.4 Summary

Reflecting on the results of this study, the author concludes that there is a pressing public health need for both new paediatric ARVs and new formulations of existing paediatric ARVs. The most effective way for this public health need to be addressed, however, is through proactively engaging the market dynamics that drive R&D for these products.

Limited market incentives and prohibitive regulatory constraints represent the major barriers to investment in this area. Partnership opportunities exist however that could make the market for paediatric ARVs more attractive to industry through risk and cost sharing with the public sector. Success in the area of product development for TB and malaria suggest that these mechanisms are both viable and desirable.

Initiatives whereby the public sector share in the R&D costs (by providing capital) and risks (by providing reward incentives and advanced market commitments) in exchange for price concessions in place of strategic public health importance could facilitate R&D in the area of paediatric ARVs.

This report recommends that multilateral donor organizations (like UNITAID) engage directly with the pharmaceutical industry by creating a Health Impact Fund (that rewards industry for changes in health outcomes), Advanced Market Commitments (for products of strategic public health importance) and engages directly with venture capital firms by providing security for money provided to pharmaceutical companies that is invested in R&D for paediatric ARVs.

7 References

- Agle, B.R., Mitchell, R.K. & Sonnenfeld, J.A., 1999. Who Matters to CEOs An Investigation of Stakeholder Attributes and Salience, Corporate Performance, and CEO Values. *The Academy of Management Journal*, 42(5), 507-525.
- Altrichter, H., 1993. *Teachers Investigate Their Work: An Introduction to the Methods of Action Research* 1st ed., Routledge.
- Andersen, R.M., 1995. Revisiting the behavioral model and access to medical care: does it matter *Journal of Health and Social Behavior*, 36(1), 1-10.
- Bogdan, R. & Biklen, S.K., 2006. *Qualitative Research for Education: An Introduction to Theories and Methods*, 5th ed., Allyn & Bacon.
- Buse, K. & Walt, G., 2000a. Global public-private partnerships: Part I--A new development in health? *Bulletin of the World Health Organization*, 78(4), 549-561.
- Buse, K. & Walt, G., 2000b. Global public-private partnerships: Part II--What are the health issues for global governance? *Bulletin of the World Health Organization*, 78(5), 699-709.
- Buse, K. & Harmer, A.M., 2007. Seven habits of highly effective global public-private health partnerships: practice and potential. *Social Science & Medicine* (1982), 64(2), 259-271.
- Cohen/Lawrence, 2007. *Research Methods in Education* 6th ed., Routledge.
- Cook, T.D. & Campbell, D.T., 1979. *Quasi-Experimentation: Design and Analysis Issues for Field Settings*, Wadsworth Publishing.

Cooper, D.R. & Schindler, P.S., 2008. Business Research Methods 10th ed., McGraw Hill Higher Education.

Denzin, N., 2006. Sociological Methods: A Sourcebook, Transaction Publishers.

Dionisio, D. et al., 2006. Affordable antiretroviral drugs for the under-served markets: how to expand equitable access against the backdrop of challenging scenarios? Current HIV Research, 4(1), 3-20.

Drucker, P.F., 1988. The coming of the new organization, Harvard Business School.

Fassinou, P. et al., 2004. Highly active antiretroviral therapies among HIV-1-infected children in Abidjan, Côte d'Ivoire. AIDS (London, England), 18(14), 1905-1913.

Freeman, R.E., 2010a. Strategic Management: A Stakeholder Approach, Cambridge University Press.

Freeman, R.E., 2010b. Strategic Management: A Stakeholder Approach, Cambridge University Press.

Friedman, M., 1962. Capitalism and Freedom 40th ed., Chicago University Press.

Gardner, J.R. & Rachlin, R., 1986. Handbook of Strategic Planning 99th ed., John Wiley & Sons Inc.

Goodpaster, K.E., 1988. Business ethics and stakeholder analysis, Division of Research, Harvard Business School.

Grant, R.M., 2001. Contemporary Strategy Analysis: Concepts, Techniques, Applications: Instructor's Manual 4th ed., Blackwell.

Hale, V.G., Woo, K. & Lipton, H.L., 2005. Oxymoron no more: the potential of nonprofit drug companies to deliver on the promise of medicines for the developing world. *Health Affairs (Project Hope)*, 24(4), 1057-1063.

Handy, C., 2002. What's a Business For?, *Harvard Business Review*.

Heywood, M., 2002. Drug access, patents and global health: chaffed and waxed sufficient. *Third World Quarterly*, 23(2), 217-231.

Karki, D. et al., 2007. Costs of a successful public-private partnership for TB control in an urban setting in Nepal. *BMC Public Health*, 7(1), p.84.

Krupp, K. & Madhivanan, P., 2009. Leveraging human capital to reduce maternal mortality in India: enhanced public health system or public-private partnership? *Human Resources for Health*, 7(1), p.18.

Lim, M.K., 2005. Transforming Singapore health care: public-private partnership. *Annals of the Academy of Medicine, Singapore*, 34(7), 461-467.

Martins, J., Loubser, M. & Van Wyk, H., 1996. *Marketing Research: A South African Approach*, Pretoria: UNISA press.

McKee, M., Edwards, N. & Atun, R., 2006. Public-private partnerships for hospitals. *Bulletin of the World Health Organization*, 84(11), 890-896.

Minford, P., 1998. *Markets not stakes : the triumph of capitalism and the stakeholder fallacy* / Patrick Minford, London :: Orion.

Nishtar, S., 2004. Public - private 'partnerships' in health - a global call to action. *Health Research Policy and Systems / BioMed Central*, 2(1), p.5.

Njau, R. et al., 2009. Implementation of an insecticide-treated net subsidy scheme under a public-private partnership for malaria control in Tanzania - challenges in implementation. *Malaria Journal*, 8(1), p.201.

Pearce, J., 2008. *Formulation, Implementation and Control of Competitive Strategy* 11th ed., McGraw-Hill Higher Education.

Pécoul, B., 2004. New drugs for neglected diseases: from pipeline to patients. *PLoS Medicine*, 1(1), p.e6.

Pope, C. & Mays, N., 1995. Qualitative Research: Reaching the parts other methods cannot reach: an introduction to qualitative methods in health and health services research. *BMJ*, 311(6996), 42-45.

Porter, M.E., 2004. *Competitive Strategy: Techniques for Analyzing Industries and Competitors* New edition., Free Press.

Puthanakit, T. et al., 2005. Efficacy of highly active antiretroviral therapy in HIV-infected children participating in Thailand's National Access to Antiretroviral Program. *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America*, 41(1), 100-107.

Sandelowski, M., 2000. Combining Qualitative and Quantitative Sampling, Data Collection, and Analysis Techniques in Mixed-Method Studies. *Research in Nursing & Health*, (23), 246-255.

Scheffler, R. & Pathania, V., 2005a. Medicines and vaccines for the world's poorest: Is there any prospect for public-private cooperation? *Globalization and Health*, 1(1), p.10.

Scheffler, R. & Pathania, V., 2005b. Medicines and vaccines for the world's poorest: Is there any prospect for public-private cooperation? *Globalization and Health*, 1(1), p.10.

Sloan, A.P., McDonald, J. & Stevens, C., 1998. My Years with General Motors Reissue., Bantam Doubleday Dell Publishing Group.

Smith, A. 1776. An Inquiry into the Nature and Causes of the Wealth of Nations., W. Strahan and T. Cadell, London

Thind, A. & Andersen, R., 2003. Respiratory illness in the Dominican Republic: what are the predictors for health services utilization of young children? Social Science & Medicine (1982), 56(6), 1173-1182.

Vian, T. et al., Public-private partnerships to build human capacity in low income countries: findings from the Pfizer program. Human Resources for Health, 5, 8-8.

Wheeler, C. & Berkley, S., 2001a. Initial lessons from public-private partnerships in drug and vaccine development. Bulletin of the World Health Organization, 79(8), 728-734.

Wheeler, C. & Berkley, S., 2001b. Initial lessons from public-private partnerships in drug and vaccine development. Bulletin of the World Health Organization, 79(8), 728-734.

Winstanley, D., Sorabji, D. & Dawson, S., 1995. When the pieces don't fit: A stakeholder power matrix to analyse public sector restructuring. Public Money & Management, 15(2), p.19.

WHO., 2011. Treatment of children living with HIV. World Health Organization webpage [<http://www.who.int/hiv/topics/paediatric/en/>] last accessed on 19 April 2011

8 Appendices

Appendix 1 Letter to participants

Dear [enter name]

I am a medical doctor working for the World Health Organization / UNITAID and am currently doing a part time MBA degree through UNISA. As part of my course requirements, I am conducting research into “Collaborative and Partnership Opportunities in the Area of Research and Development for Paediatric Antiretroviral Drugs for Low Income Countries”.

If you are agreeable, I would like to interview you for about half an hour with a view to collecting data for this research project. It will be a semi-structured interview that examines 1) the public health needs, 2) stakeholder interests and 3) partnership logic in this area. All interviews will be recorded and transcribed before analyzed and written up in a final report. Please find attached the interview protocol that will be used in this study.

Please let me know if you are willing to participate and feel free to ask me any questions that might help clarify the research process being undertaken.

Your sincerely,

Dr Greg Martin

Technical officer: WHO/UNITAID

Appendix 2 Interview protocol

All interviews in this study will be conducted with 1) informed consent of the participants, and 2) impartiality (that is to say, the interviewer will respect the thoughts and opinions of the participant and not try to influence the outcome of the study by prompting the interviewee with preformed answers)

The interview process will include:

1. A polite greeting. The participant will be thanked for his or her time
2. A confirmation that the interviewee is willing to participate and understands the nature of the study
3. A commitment to confidentiality. That is to say that while the information given will be described in the outcomes of the study, the information will not be attributed to a particular participant unless specific permission to do so is given
4. The purpose and objectives of the study will be reiterated
5. The participant will be given an opportunity to ask any questions about the study before the interview begins.
6. The participant will be asked for confirmation of their permission to have the interview recorded and then transcribed.
7. The participant will then be asked to address, in his or her own words, each of the study objectives in turn.
8. The interviewee will ask questions that help him understand the comments made or for clarity on the issues raised
9. The participant will be thanked for his time once again and asked if he or she has anything to add
10. The interview will be transcribed and analyzed as per the study design protocol

Appendix 3 Global commitment to addressing access to ARVs for children

Commitments made by multilateral agencies and governments

1. **MDGs** – Goal of a 2/3 reduction in mortality rate for children under the age of 5
2. **UNGASS declaration for commitment on HIV/AIDS** – New resolution in Oct 2005 on universal access calls for governments to come “as close as possible to the goal of universal access to treatment by 2010 for all those who need it”
3. **UN General Assembly - A World Fit for Children** – identified HIV as one of 4 priority areas
4. **G8 Declaration issued at Gleneagles** - Universal access to ART for all by 2010
5. **UN Secretary General** – “United for Children”: a campaign with UNICEF and UNAIDS called for access to treatment for 80% of HIV infected children by 2010
6. **MDGs** – Goal of a 2/3 reduction in mortality rate for children under the age of 5

Appendix 4 Product Development Partnerships

International product development partnerships and public–private partnerships include:

1. The [Drugs for Neglected Diseases Initiative](#) (DNDi) was founded in 2003 as a not-for-profit drug development organization focused on developing novel treatments for patients suffering from neglected diseases.
2. [Aeras Global TB Vaccine Foundation](#) is a PDP dedicated to the development of effective [tuberculosis](#) (TB) vaccine regimens that will prevent TB in all age groups and will be affordable, available and adopted worldwide.
3. FIND [\[1\]](#) is a Swiss-based non-profit organization established in 2003 to develop and roll out new and affordable diagnostic tests and other tools for poverty-related diseases.
4. The [Global Alliance for Vaccines and Immunization](#) is financed per 75% (750 Mio.US\$) by the [Bill and Melinda Gates Foundation](#), which has a permanent seat on its supervisory board.
5. [The Global Fund to Fight AIDS, Tuberculosis & Malaria](#), a [Geneva](#)-based UN-connected organisation, was established in 2002 to dramatically scale up global financing of interventions against the three pandemics.
6. The [International AIDS Vaccine Initiative](#) (IAVI), a biomedical public–private product development partnership (PDP), was established in 1996 to accelerate the development of a vaccine to prevent HIV infection and AIDS. IAVI is financially supported by governments, multilateral organizations, and major private-sector institutions and individuals.
7. The [International Partnership for Microbicides](#) is a non-profit product development partnership (PDP), founded in 2002, dedicated to the development and availability of safe, effective microbicides for use by women in developing countries to prevent the sexual transmission of HIV. See also [Microbicides for sexually transmitted diseases](#).
8. [Medicines for Malaria Venture \(MMV\)](#) is a not-for-profit drug discovery, development and delivery organization, established as a Swiss foundation in 1999, based in [Geneva](#). MMV is supported by a number of foundations, governments and other donors.
9. The [TB Alliance](#) is financed by public agencies and private foundations, and partners with research institutes and private pharmaceutical companies to develop faster-acting, novel treatments for tuberculosis that are affordable and accessible to the developing world.
10. A UN agency, the [World Health Organization](#) (WHO), is financed through the UN system by contributions from member states. In recent years, WHO's work has involved more collaboration with NGOs

and the pharmaceutical industry, as well as with foundations such as the Bill and Melinda Gates Foundation and the Rockefeller Foundation. Some of these collaborations may be considered global public–private partnerships (GPPPs); half of the WHO budget is financed by private foundations.

11. The [United Nations Foundation](#) & Vodafone Foundation Technology Partnership, a five-year, \$30 million commitment, leverages the power of mobile technology to support and strengthen humanitarian work worldwide. Partners include the [World Health Organization](#) (WHO), DataDyne, the mHealth Alliance, the [World Food Program](#) (WFP), Telecoms Sans Frontieres, and the UN Office for the Coordination of Humanitarian Affairs (OCHA).

Appendix 5 Mismatch between demand and supply of health services and medication

Mismatch	Description
Lack of information (patients)	The HIV status of individuals may not be known. HIV positive people or their caregivers may not know about the availability of treatment.
Lack of information (clinicians)	Paediatric ARVs have to be prescribed by a provider with some training. A lack of capacity may widen the gap between need and supply
Lack of information (supply organizations)	Poor demand forecasting and poor characterization of markets prevents supply companies from planning production
Cost (to patient)	Even if ARVs are given free, associated costs may be prohibitive (and even catastrophic), e.g. user fees, testing costs, transport costs.
Cost (to the system)	The “demand” for drugs is driven by managers who are not the end users (those with the “need”). There is therefore a mismatch between need and demand.
Barriers to competition	Complexity in R&D and regulatory issues makes it very difficult for new comers to enter into the market.
Externalities	Some economists distinguish between “selfish” and “caring” externalities. Selfish externalities can affect demand, for example, in willingness to pay for a child’s care. Some people benefit from knowing that others are receiving care (caring externalities). This has implications for tax.
Market incentives (profit)	Industry and the market driving the supply of these drugs may be profit driven, hence even in the face of a given demand, they might not respond with supply if it does not represent a profitable scenario
Non-market incentives (government provided services)	Public programmes typically try to match need with supply. However, where patients have to demand service to receive it, ignoring demand and matching supply with “need” can lead to excess in supply, waste and eventual shortages.

Appendix 6 UN and UN Agency resolutions pertaining to technology transfer

Technology Transfer for local production of HIV related drugs in African countries:

In April 2001, the 57th session of the UN Commission on Human Rights adopted Resolution 2001/33, on “Access to Medication in the Context of Pandemics such as HIV/AIDS”. The Commission calls upon States, at the international level, to take steps individually and or through international co-operation, in accordance with applicable international law, including international agreements acceded to, such as to facilitate access in other countries to essential preventative, curative or palliative pharmaceuticals or medical technologies used to treat pandemics such as HIV/AIDS or the most common opportunistic infections that accompany them wherever possible, especially in times of emergency.

On 21st May 2001, the 54th World Health Assembly in the resolution “Scaling Up the Response to HIV/AIDS” (WHA 54,10), recalled “efforts to make drugs available at lower prices for those in need” and urged Member States “in constructively in strengthening pharmaceutical policy and practices, including those applicable to generic drugs and intellectual property regimes, in order to promote innovation and the development of domestic industries consistent with national law”

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The WTO DOHA Declaration reaffirms the commitment of developed countries to provide incentives to its industry for transfer of pharmaceutical technology to least developed countries.

Appendix 7 Examples of technology transfer projects

The Democratic Republic of Congo:

Pharmakina (PK), originally owned by Boehringer Mannheim and Roche respectively, was taken over by the management of PK at the beginning of 1999. PK is not only the largest private employer in Eastern Congo, but also the world largest produce of quinine. PK has put into operation a diagnostic centre for malaria, TB and pregnancy tests which is already open to the public. It also operates 12 Health Centres spread over other and South Kivu.

The aim of this humanitarian project is to reduce the mobility and mortality of AIDS patients in Bukavu, Eastern Congo by offering cost effective diagnostics and low priced ARVS which are today's best available choices for fix dosed combinations of stavudine, lamivudine and nevirapine and is taken as bi-daily tables. It is well tolerated in most cases, has few contra indications and is appropriate for use in women of child bearing age. It has proven efficacy under actual field conditions, is affordable and is easy to take.

This is part of an on-going PPP in association with the German Agency for Technical Cooperation (GTZ that will include the screening, counseling and therapy of patients. A total sum of around USD 1 million was invested.

Action medeor works in close partnership with Pharmakina by providing treatment to a minimum of 50 to 100 patents and monitoring of 250 to 500 patients. It has appointed a project manager who will be responsible for the implementation of anti-retroviral therapy. Laboratory has been equipped with flow cytometer and the training of personnel has been provided (Dionisio et al. 2006)

Tanzania

Tanzania Parmaceutical Industries (TPI), a pharmaceutical manufacturing company , 40% owned by government, 60% by private entrepreneurs, having its operations in Arusha has teamed up to manufacture artemisinin-based anti-malarial drugs at affordable prices. Because Tanzania is on of the countries hardest hit by HIV/AIDS, Tanzania has decided to start manufacturing life-prolonging drugs for AIDS patients. Since the country has an acute shortage of highly qualified technical and industrial pharmacists, TPI has entered into an agreement with experts from Thailand who have agreed to cooperate and transfer knowledge and know-how and all the necessary information to support the production of pharmaceutical and in particular anti-malarials, antiretrovirals, and anti-TB drugs.